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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/941,492	08/29/2001	Lloyd G. Mitchell	31304-B-A-E 069906.0106	7149

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EXAMINER	
EPPS FORD, JANET L	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,492	MITCHELL ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments

Claim Rejections - 35 USC § 112

2. Claims 1-17 and 35-39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for producing a chimeric mRNA in a cell *in vitro*, does not reasonably provide enablement for producing a chimeric in a cell *in vivo* for therapeutic treatment of conditions associated with human papilloma virus pre-mRNA expression in a cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record in the office action mailed 5-05-04.

3. Applicant's arguments filed 11-08-04 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification provides support and guidance for one of skill in the art to make and use the full scope of the claimed invention without undue experimentation. According to Applicants the specification discloses producing chimeric RNA in a variety of cells including 293 cells, and HPV-infected cancer cells such as SiHa and CaSki cells. According to Applicants Example 14 of the of the specification discloses mouse model for papilloma infections using a xenograft technique, and discuses how to create the model, what cells and viruses can be used, and clearly states that the disclosed animal model is used to test the *in vivo* efficacy of the anti-papillomavirus PTMs.

Therefore, according to Applicants the specification clearly enables for *in vivo* application of the presently claimed nucleic acids and cells.

In response to Applicant's assertions, it is noted that Applicants provide only *in vitro* evidence of the efficacy of the claimed invention. In regards to the *in vivo* use of the cells and nucleic acid molecules of the instant invention, Applicants provide only prophetic guidance for using an *in vivo* mouse model for papilloma infections to test the *in vivo* efficacy of the anti-papillomavirus PTMs of the instant invention. Applicants have not provided any evidence that the claimed methods of use, cells, and nucleic acids can be used to treat human papilloma infections *in vivo*. According to Applicant's the compositions of the instant invention can be tested *in vivo*, however a mere test for efficacy does not provide evidence of efficacy. Moreover, in regards to the *in vitro* expression of anti-papillomavirus PTMs in 293 cells, Applicants have not provided a specific correlation between the *in vitro* expression of the PTMs of this invention, and the treatment of human papillomavirus infections *in vivo*. Moreover, applicants have not provided any guidance regarding how to overcome the various factors that are known in the art to complicate the gene therapy art, i.e. the expression of the nucleic acid molecules of the invention for therapeutic purposes. As stated in the prior Office Action, "[t]here are a variety of factors that complicate the gene therapy art which have not been overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the in vivo consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein

produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, the subject it is administered to, and the disease being treated."

Applicants make reference to recent teachings to provide evidence of enablement for the *in vivo* use of PTMs targeted to human papilloma virus (Bhaumik, 2004), Factor VIII (Chao, 2003) and hyper-IgM X-linked immunodifficiency (Tahara et al., 2004). However, the instant specification claims priority back to 12/15/1995, and at the time the invention was made, the state of the prior art indicated that efficient delivery and expression of foreign DNA was not yet achieved by any method (Marshall, Science, 269:1050-1055, August, 1995). See MPEP § 2164.05 that states "[T]o overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing." At the time of the instant invention the teachings of Bhaumik, Chao, and Tahara et al. was not known the skilled artisan, such that the skilled artisan would have been capable of using (at the time of filing) the claimed compositions and methods for treating a disease in a human comprising the administration of vectors which produce the PTMs of the instant invention.

As stated in the prior Office Action, the quantity of experimentation required to practice the claimed invention would encompass determining means such that all pre-trans-splicing molecules are all expressed in the same diseased cells at the same time and for a sufficient period of time such that the desired chimeric mRNA molecule is produced in a therapeutic amount to correct the defect in the diseased cells. In response to this position made by the Examiner, Applicants argued that the delivery of every PTM to every cell for expression of every PTM to

promote trans-splicing is not required to confer a therapeutic benefit. Moreover, according to Applicants, various conditions can be corrected with low levels of trans-splicing. Again, Applicants made reference to the teachings of Bhaumik (2004), Chao (2003), and Tahara (2004) to support their assertions. It is first noted that this was not the position set forth by the examiner in the prior Office Action. To clarify the examiner's original position, to practice the claimed invention the skilled artisan would have to devise means such that the pre-trans-splicing molecules are present in the appropriate cells, such that when the target pre-mRNA is produced the PTMs are available to utilize the cell's splicing machinery to produce the chimeric molecules of the present invention, wherein the chimeric molecules function to produce the therapeutic benefit. In response to Applicant's assertions, again it is noted that Applicants are relying upon post-filing data support their arguments. However, the teachings set forth in the Bhaumik (2004), Chao (2003), and Tahara (2004) references were not incorporated into the body of the specification as originally filed. It remains that the instant claims read on a method of gene therapy, however Applicants have not provided a sufficient correlation between the *in vitro* production of chimeric RNA molecules using the PTMs of the instant invention, and the production of a therapeutic effect in a human. Moreover, the prophetic teachings regarding how to test the compounds of the instant invention for efficacy in an animal model does not provide evidence of *in vivo* efficacy of the PTMs or chimeric RNAs of the instant invention.

Therefore, it is concluded that the amount of experimentation required for the skilled artisan to practice the full scope of the claimed invention would be undue based upon the known unpredictability regarding the efficient delivery of gene therapy constructs *in vivo* and further with the production of secondary effects such as treating a disease associated with the expression

of a gene, and the lack of guidance in the specification as filed in this regard. The quantity of experimentation required to practice the invention as claimed would require determining modes of delivery in a whole organism such that the expression of a single gene is replaced and the desired secondary effect (treating a patient with a disease associated with the expression of the papilloma virus gene) is obtained. The specification as filed provides no specific guidelines in this regard. The deficiencies in the specification would constitute undue experimentation since these steps must be achieved without instructions from the specification before one is enabled to practice the claimed invention.

Double Patenting

4. Claim(s) 1-39 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent No. 6,013487 in view of Hendricks et al. (US Patent No. 5,580,970 A), for the reasons of record set forth in the prior Office Action.

5. Applicant's arguments filed 11-08-2004 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that Applicants will submit a terminal disclaimer, if appropriate, once Applicants have successfully overcome the remaining outstanding rejections and the Examiner has indicated allowance of claims. Moreover, Applicants further submit that the claims of the present invention are not anticipated by or obvious over the claims of Hendricks et al. Hendricks does not claim the cells, nucleic acids or methods of the present invention and cannot be used in combination with another reference in a double patenting rejection. First, it is noted that the instant rejection is not a provisional rejection, and Applicants may not hold responses to non-provisional rejections in abeyance (See

37 CFR 1.111), Applicant's reply must present arguments pointing out the specific distinctions believed to render the claims, including any newly presented claims, patentable over any applied references. In the instant case Applicants have not provided any arguments regarding how the claims of US Patent No. 6,013,487 do not render obvious the claimed invention in combination with the teachings of Hendricks et al. Applicants merely point out the differences between the instant invention and Hendricks et al., however this reference was provided as a supporting reference for its disclosure of a variety of nucleotide sequences that are useful for the detection of human papillomavirus (HPV) mRNA or DNA in cells (see col. 3, lines 48-58). Hendricks et al., also teach that there is a close association between HPV and cervical carcinoma (see col. 3, lines 48-55). See Figures 3-4 for a structural description of specific nucleotide sequences that are useful for binding HPV nucleic acid in cells. As stated in the prior Office Action, the claims of the issued US Patent 6,013,487 in view of Hendricks et al. was considered to render obvious the instantly claimed invention. Applicants have not addressed how the combination of these two references renders obvious the instantly claimed invention.

Conclusion

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37

CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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